Clinical Nutrition xxx (2015) 1–7

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

The famine exposure in early life and metabolic syndrome in adulthood

Ningjian Wang [a], Xiaojin Wang [b], Qin Li [a], Bing Han [a], Yi Chen [a], Chunfang Zhu [a], Yingchao Chen [a], Dongping Lin [a], Bingshun Wang [b], Michael D. Jensen [c, **], Yingli Lu [a, *]

[a] Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China
[b] Department of Biostatistics, Shanghai Jiaotong University School of Medicine, Shanghai, China
[c] Endocrine Research Unit, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Article history:
Received 14 August 2015
Accepted 16 November 2015

Keywords:
Famine
Metabolic syndrome
Sex specific
Early life

SUMMARY

Background & aims: Epidemiologic studies have revealed that early-life conditions influence later risk of chronic diseases. We aimed to explore whether exposure to Chinese famine between 1959 and 1962 during fetal and childhood period was related with metabolic syndrome (MS) in adulthood.
Methods: 6445 subjects from SPECT-China study were divided into fetal-exposed (1959–1962), childhood-exposed (1949–1958), adolescence/young adult-exposed (1921–1948), non-exposed (1963–1974) and non-exposed (after 1975). MS was defined by the International Diabetes Federation criteria.
Results: The prevalences of MS in the non-exposed (1963–1974), fetal and childhood-exposed were 16.4%, 20.1% and 19.1% in men and 13.5%, 23.7% and 33.5% in women, respectively. After adjustment for age, compared with non-exposed (1963–1974), fetal and childhood-exposed women had significantly higher prevalences of MS ($P < 0.05$), but not in men. Famine exposure during the fetal period (OR 1.47, 95% CI 1.05, 2.07) and childhood (OR 1.80, 95% CI 1.22, 2.67) was associated with higher risk of MS in women after adjusting for age (both $P < 0.05$). Further adjustments for age, smoking, rural/urban residence and economic status did not significantly attenuate this association.
Conclusions: Exposure to famine in early life had sex-specific association with MS. It also suggests the adverse effects of malnutrition might extend beyond the 'first 1000 days' and last 9 years.

1. Introduction

Metabolic syndrome (MS) comprises a group of disorders, including abdominal obesity, hypertension, dyslipidemia and dysglycemia that increase the risk of multiple chronic diseases [1]. According to a national survey in 2009, the MS prevalence ranges from 10.5% to 21.3% based on different definitions [2].

In the past decades, extensive epidemiologic studies have revealed that early-life conditions, such as nutrition, influence later risk of noncommunicable chronic diseases, including metabolic diseases [3,4]. Undernutrition in early life may participate in the origins and development of abdominal obesity [5], insulin resistance [6], hyperglycemia [7,8], hypertension [9] and hyperlipidemia [10], all of which are the metabolic syndrome components.

The famine in China from 1959 to 1962, called China's Great Famine is considered to be the largest and most severe famine during the 20th century [11]. About 20–30 million excess deaths was caused by the famine [12]. It is a catastrophe in human history, but now it is a valuable chance to investigate the relationship between famine exposure and MS in Chinese. In China, just two studies examined this association and revealed a significant association between famine exposure during fetus and infancy and higher risk of MS in adulthood [13,14], though the only study

Abbreviations: BP, blood pressure; IDF, International Diabetes Federation; GDP, gross domestic product; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; BMI, body mass index; HOMA-IR, homeostatic model assessment-insulin resistance; MS, metabolic syndrome; TG, triglycerides; FPG, fasting plasma glucose.

* Corresponding author. Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200011, China. Tel.: +86 13636352507; fax: +86 21 63136856.
** Corresponding author. Endocrine Research Unit, 5-194 Joseph, Mayo Clinic, Rochester, MN 55905, USA. Tel.: +1 507 255 6515; fax: +1 507 255 4828.
E-mail addresses: jensen@mayo.edu (M.D. Jensen), luyingli2008@126.com (Y. Lu).

http://dx.doi.org/10.1016/j.clnu.2015.11.010

based on Dutch Famine found no significant association [15]. In these studies, they used ATP III [16] and Chinese Diabetes Society criteria [14]. In the Chinese, International Diabetes Federation (IDF) criteria is another definition predicting cardiovascular disease and diabetes risk [17], which has not been studied. Moreover, one of them explored sex-specific effect of famine exposure, but it was just conducted in one city and its data source was clinic-based, which may not be generalizable to other areas in China [14]. Also, van Abeelen et al.'s study indicated the adverse effect of undernutrition on diabetes could extend beyond the 'first 1000 days' [18], but no study explored this extension existed in MS after famine exposure.

Hence, in 2014 we performed an investigation called the **S**urvey on **P**revalence in **E**ast **C**hina for Me**t**abolic Diseases and Risk Factors (SPECT-China). We aimed to explore the relationship between famine exposure in early life and sex-specific risk of MS based on the IDF definition in a general Chinese population.

2. Methods

2.1. Study population

East China consists of Shanghai and 7 provinces and had a population of approximately 395 people million in 2011, accounting for 29.2% of the population of China. Of these, 99.5% of the residents are Han Chinese. SPECT-China is a population-based cross-sectional investigation in East China in 2014 [8,19]. The registration number is ChiCTR-ECS-14005052, http://www.chictr.org.cn. A stratified cluster sampling method was applied to choose a sample of persons ≥18 years old in the general population. Stratification level was rural/urban area and current economic status in Shanghai, Jiangxi Province and Zhejiang Province (Fig. 1). In urban areas, we randomly chose 1 city with a low economic status and 1 city with a high economic status. Then, in both cities, we randomly chose 3 districts from which 3 communities were randomly selected. Because the 3 communities chosen in Jiangxi Province were all very large communities, to maintain the study feasibility and to avoid oversampling in this area, we randomly chose 1 community (3 study spots) from these 3 communities. In rural areas we randomly chose 6 villages with low economic status and 6 villages with high economic status. This study was performed in 3 urban sites in Shanghai, 1 urban site in Jiangxi Province, 3 rural sites in Shanghai, 3 rural sites in Zhejiang and 6 rural sites in Jiangxi Province (Supplementary Fig. S1). We advertised our investigation by cooperation with village and community administrators of residence registration. Participants were invited by providing the information of this investigation through house-to-house visit. Chinese citizens ≥18 years old lived in their current area for ≥6 months were selected. Subjects with severe communication problems, acute illness and an unwillingness to participate were excluded. 7927 individuals were selected, and 7200 people participated in this investigation. The overall response rate was 90.8%. 727 Persons declined during the days when the investigation was carried out because of various unknown or known reasons, such as business, having had breakfast, unwillingness, etc. The overall response rate was 90.8%. Age and location of residence were comparable between the subjects declined and enrolled. We also excluded subjects who missed lab (n = 183) and questionnaire data (n = 112), and were <18 years old (n = 6). In total, 6899 subjects were included in the SPECT-China study (Fig. 1).

After excluding participants who had missing values of waist circumference (n = 364), lipid profile (n = 3) and blood pressure (BP) (n = 87), 6445 subjects were included in this study (Fig. 1). The Ethics Committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine approved this study. All participants provided written informed consent before data collection. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Anthropometric, and laboratory measurements

Information on the demography, medical history and lifestyle risk factors was collected by trained staff. Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarette [20]. Weight, height, waist circumference and BP were assessed by standard methods [20]. Central obesity was considered if waist circumference ≥90 cm in men or ≥80 cm in women [21]. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Venous blood samples were obtained after fasting for at least 8 h. The blood samples for the plasma glucose test were centrifuged within 1 h after collection. Fasting plasma glucose (FPG), triglycerides (TG) and high density lipoprotein (HDL) were assessed by Beckman Coulter AU 680 (Germany). Insulin was measured by chemiluminescence method (Abbott i2000 SR, USA). Insulin resistance was estimated by HOMA-IR: [fasting insulin (mIU/L)] × [FPG (mmol/L)]/22.5.

2.3. Exposure age and area categories

Famine exposure is set up on a proxy, the birth year. The famine period was between 1959 and 1962 [22]. Based on the study by van Abeelen et al. [18], subjects were divided into five groups based on their ages when exposed to famine from January 1, 1959 to December 31, 1962: fetal period (age 52–55 yrs, birth year 1959–1962) (n = 701), childhood (age 56–65 yrs, birth year 1949–1958) (n = 1776), adolescence and young adult (age 66–93 yrs, birth year 1921–1948) (n = 1053), non-exposed (age 40–51 yrs, birth year 1963–1974) (n = 1719) and non-exposed (age ≤39 yrs, birth year after 1975) (n = 1196) [8]. In order to choose the middle-aged as the reference, we separated the non-exposed group into two groups: age 40–51 yrs (reference) and age ≤39 yrs. Childhood between age 0 and 9 years is a period of rapid growth in physiology, behavior, and cognition [18,23]. Adolescence and young adulthood are characterized by a growth spurt, sexual development, and gradual realization of physiological homeostasis [18,23].

GDP per person is often considered an indicator of living standard of an area and general population [23]. Current economic status was measured by the GDP per capita in 2013 at each site [7]. Each of the 16 study sites was allocated to high or low economic status in comparison with the GDP per capita of the whole nation (6807 US dollars from World Bank) in 2013. Rural/urban residence was also chosen as one of the covariates, because people living in rural or urban area tend to have different prevalences of MS [24].

2.4. The definition of MS

MS was determined based on the International Diabetes Federation criteria (2005) [21]. A person with MS must have: abdominal obesity (waist circumference: male ≥90 cm, female ≥80 cm, or BMI is ≥30 kg/m^2) plus any two of the following four parameters: (i) Raised TG ≥ 1.7 mmol/L, or treatment for this dyslipidemia; (ii) Reduced HDL-C <1.03 mmol/L in men or <1.29 mmol/L in women, or treatment for this dyslipidemia; (iii) Raised BP: systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, or

Please cite this article in press as: Wang N, et al., The famine exposure in early life and metabolic syndrome in adulthood, Clinical Nutrition (2015), http://dx.doi.org/10.1016/j.clnu.2015.11.010

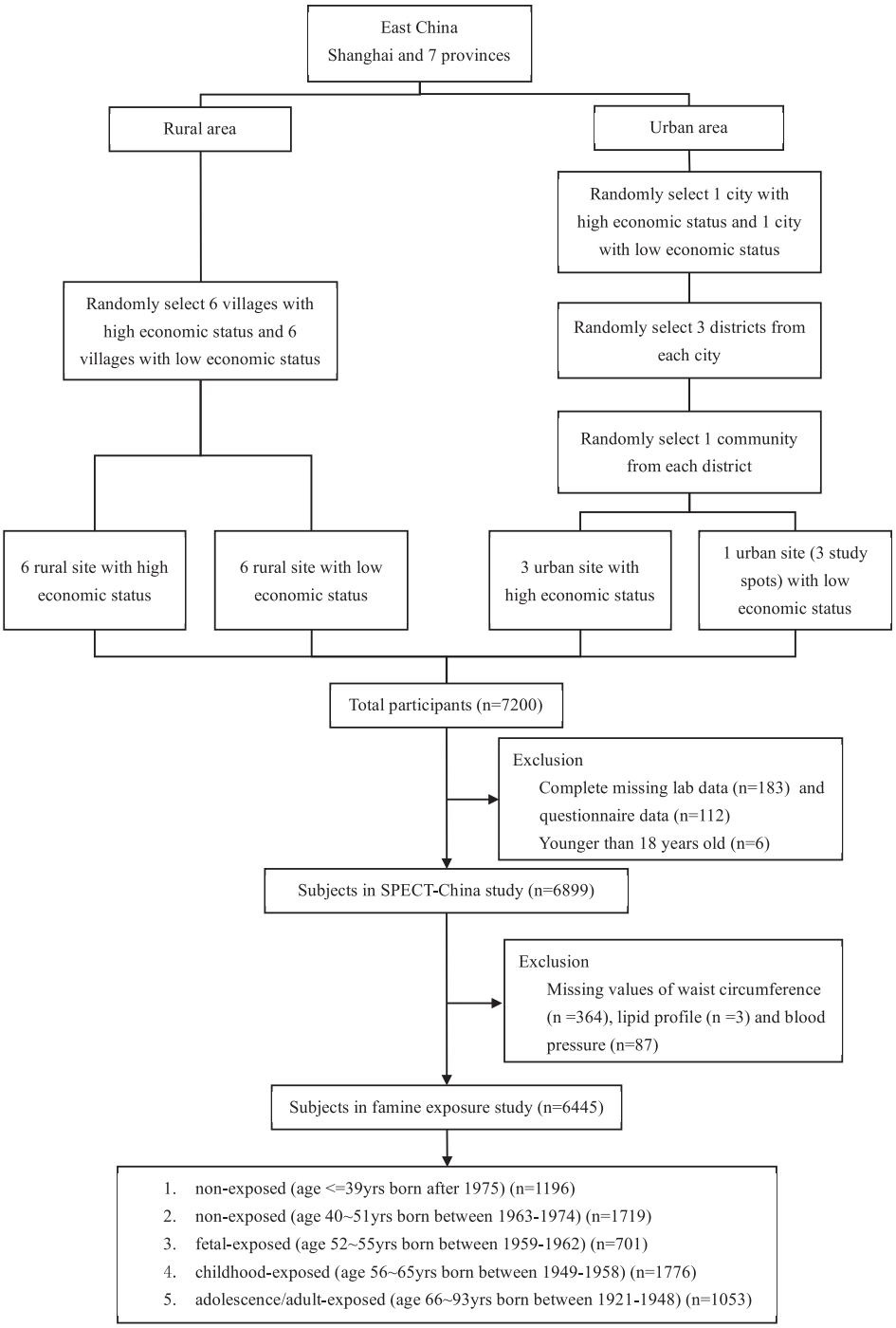

Fig. 1. Flowchart of sampling frame and participants selected from SPECT-China.

treatment of hypertension; (iv) Raised FPG ≥5.6 mmol/L or a history of type 2 diabetes.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, Version 22 (IBM Corporation, Armonk, NY, USA). All analyses were two-sided. $P < 0.05$ was considered significant. Continuous and categorical variables were expressed as the mean ± standard deviation (SD) and a percentage (%), respectively. Characteristics of the study sample were compared by analysis of covariance. Age-adjusted *P* value was given.

To analyze the relationship among life stages when exposed to famine, rural/urban areas, economic status and risk of diabetes in adulthood, logistic regression analysis was used. Separate males and females were analyzed. Non-exposed (1963–74) was the reference. Model 1 was adjusted for age. Model 2 was adjusted for age, rural/urban residence, economic status and current smoking. The interaction between life stages when exposed to famine and economic status and rural/urban

Please cite this article in press as: Wang N, et al., The famine exposure in early life and metabolic syndrome in adulthood, Clinical Nutrition (2015), http://dx.doi.org/10.1016/j.clnu.2015.11.010

residence was analyzed by adding a multiplicative factor in the logistic regression model. Data were expressed as odds ratio (OR) (95% confidence interval).

3. Results

3.1. Sex-specific characteristics of participants by life stages when exposed to famine

The results of MS components by life stages when exposed to famine are summarized in Table 1. In men, compared with non-exposed (birth year 1963–74), fetal- or childhood-exposed subjects had significantly greater waist circumference, FPG and HDL (all age-adjusted $P < 0.05$) but comparable HOMA-IR and lower TG. In women, however, fetal- and childhood-exposed subjects had significantly higher waist circumference, TG, systolic BP and greater HOMA-IR (all age-adjusted $P < 0.05$).

3.2. Sex-specific prevalence of MS components by life stages when exposed to famine

The sex-specific prevalences of MS components are showed in Table 2. Fetal- or childhood-exposed men had significantly higher prevalence of abdominal obesity and raised FPG (age-adjusted $P < 0.05$), compared with non-exposed (birth year 1963–74). In women, fetal- or childhood-exposed subjects had significantly higher prevalence of abdominal obesity, raised FPG, raised TG and raised BP (all age-adjusted $P < 0.05$).

The prevalences of MS in the non-exposed (1963–1974), fetal and childhood-exposed were 16.4%, 20.1% and 19.1% in men and 13.5%, 23.7% and 33.5% in women, respectively (Fig. 2). After adjustment for age, compared with non-exposed (1963–1974), fetal- and childhood-exposed men had comparable prevalence of MS (age-adjusted $P > 0.05$) but fetal- and childhood-exposed women had significantly higher prevalences of MS (age-adjusted $P < 0.05$).

We also measured the sex-specific prevalence of metabolic syndrome among subjects according to the birth years (1956–1967) (Supplementary Fig. S2). In men we could not observe some trend or progressive dose-related improvement (P for trend 0.22). In women, however, the prevalence peaked in subjects born in 1959 and there was a progressive dose-related improvement from subjects born in 1959 to those in 1962 (P for trend <0.001).

3.3. Association of life stage when exposure to famine with MS

Table 3 provides the association of famine exposure with MS. In fetal- and childhood-exposed women, the OR of MS was 1.47 (95% CI 1.05, 2.07) and 1.80 (95% CI 1.22, 2.67) (both $P < 0.05$), significantly greater than that in the non-exposed group (birth year 1963–1974) after adjusting for age (Table 3, model 1). Adjustment for smoking, rural/urban residence and economic status did not attenuate the association (Table 3, model 2) and the OR of MS reached 1.53 (95% CI 1.08, 2.17) and 1.95 (95% CI 1.30, 2.93) in fetal- and childhood-exposed women (both $P < 0.05$). No interaction was found between life stage when exposure to famine and economic status or rural/urban residence (both $P > 0.05$). There was no similar association observed among fetal or childhood-exposed males (both $P > 0.05$).

4. Discussion

In this study, a significant relationship existed between famine exposure in utero and during childhood (0–9 years) and MS defined by IDF criteria in general Chinese women, though this association was not observed in men. This study added evidence to the DOHaD (developmental origins of health and disease) hypothesis [3] and suggests the adverse effects of malnutrition might extend beyond the 'first 1000 days'.

The current study adds new and further evidence to previous studies. Based on the national survey data in 2002, Yanping Li et al. found exposure to the Chinese famine in utero and during infancy (0–2 years) is related with a higher risk of MS in adulthood [13]. The risk increased about one to two times compared with nonexposed [13]. But in that study, sex-specific analysis was not performed. In the other study in China, X Zheng et al. also demonstrated that females exposed to the Chinese famine in utero and during infancy (0–2 years) had higher risk of MS, but not males [14]. This finding is consistent with ours. However, their study population was from annual physical examinations in 2008 in one hospital in Chongqing, so selection bias may not be excluded and

Table 1
Metabolic factors of study population by life stages when exposure to famine.

	Non-exposed (1975 and later)	Fetal-exposed (1959–1962)	Childhood-exposed (1949–1958)	Adolescence/adult-exposed (1921–1948)	Non-exposed (1963–1974)
Age in 2014	≤39	52–55	56–65	66–93	40–51
Men					
N	504	309	749	467	709
Waist circumference, cm	80.1 ± 9.2	83.9 ± 9.0	83.6 ± 9.5*	83.5 ± 9.7*	82.9 ± 8.8
FPG, mmol/L	5.1 ± 1.1	5.9 ± 1.3*	5.9 ± 1.6	5.9 ± 1.3	5.6 ± 1.4
HDL, mmol/L	1.29 ± 0.25	1.36 ± 0.31	1.41 ± 0.34*	1.44 ± 0.35*	1.34 ± 0.29
Triglycerides, mmol/L	1.94 ± 2.30	1.98 ± 1.43*	1.80 ± 1.83*	1.54 ± 1.35*	2.24 ± 2.31
Systolic BP, mmHg	123 ± 16	130 ± 20	135 ± 19	143 ± 21	128 ± 18
Diastolic BP, mmHg	76 ± 11*	82 ± 12	82 ± 13	79 ± 12*	82 ± 13
HOMA-IR	1.64 ± 2.35	1.41 ± 1.30	1.49 ± 2.26	1.45 ± 2.04	1.38 ± 1.53
Women					
N	692	392	1027	586	1010
Waist circumference, cm	69.6 ± 8.0	77.4 ± 8.7*	79.6 ± 9.3*	81.6 ± 10.2	74.1 ± 8.2
FPG, mmol/L	5.1 ± 0.5	5.7 ± 1.3	5.8 ± 1.3	6.0 ± 1.5	5.4 ± 1.0
HDL, mmol/L	1.51 ± 0.29	1.52 ± 0.31	1.53 ± 0.33	1.55 ± 0.33	1.52 ± 0.31
Triglycerides, mmol/L	1.07 ± 0.65*	1.77 ± 2.22*	1.69 ± 1.17*	1.68 ± 1.28	1.31 ± 1.11
Systolic BP, mmHg	112 ± 13	130 ± 18*	135 ± 21*	144 ± 22*	122 ± 18
Diastolic BP, mmHg	70 ± 10*	79 ± 12*	78 ± 12	78 ± 12	75 ± 12
HOMA-IR	1.29 ± 0.85	1.68 ± 1.87*	1.73 ± 2.62*	1.73 ± 2.39	1.42 ± 1.28

BP, blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein.
Data were expressed as the mean ± SD. *age-adjusted $P < 0.05$, compared with non-exposed (1963–1974).

Please cite this article in press as: Wang N, et al., The famine exposure in early life and metabolic syndrome in adulthood, Clinical Nutrition (2015), http://dx.doi.org/10.1016/j.clnu.2015.11.010

Table 2
Prevalence of components of metabolic syndrome by life stages when exposure to famine.

	Non-exposed (1975 and later)	Fetal-exposed (1959–1962)	Childhood-exposed (1949–1958)	Adolescence/adult-exposed (1921–1948)	Non-exposed (1963–1974)
Age in 2014	≤39	52–55	56–65	66–93	40–51
Men					
N	504	309	749	467	709
Central obesity, %	14.3	25.2	25.6*	29.8*	23.8
Raised FPG, %	13.3*	46.3*	49.0*	54.2	30.3
Raised triglycerides, %	33.5*	48.2	37.2*	28.3*	48.0
Reduced HDL, %	12.9	13.3	10.7	9.6	13.0
Raised BP, %	35.1	59.5	67.6	81.4	53.0
Current smoker, %	31.5*	60.5	52.8	44.7*	51.7
Women					
N	692	392	1027	586	1010
Central obesity, %	11.6	38.8*	48.8*	59.2	24.8
Raised FPG, %	15.5*	37.0	50.7*	55.1	30.4
Raised triglycerides, %	9.8*	34.4*	36.8*	33.4	17.8
Reduced HDL, %	22.0	24.7	24.0	21.2*	23.8
Raised BP, %	13.0	55.9*	65.1	78.3	33.4
Current smoker, %	1.5	1.1	2.5	7.1	0.9

BP, blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein.
Data were expressed as the mean ± SD. *age-adjusted $P < 0.05$, compared with non-exposed (1963–1974).

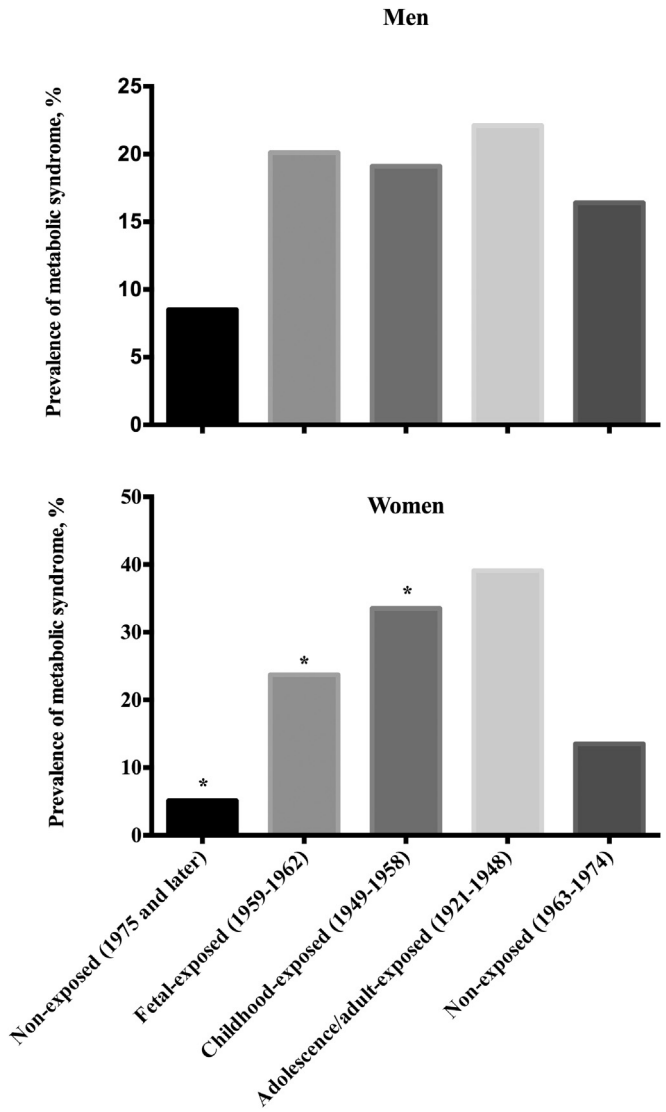

Fig. 2. Prevalences of metabolic syndrome in different life stages when exposure to famine. *age-adjusted *P* value, compared with non-exposed (1963–1974).

Table 3
Association of life stage when exposure to famine with metabolic syndrome.

	Model 1	Model 2
Men		
Non-exposed (1975 and later)	0.87 (0.51, 1.47)	0.88 (0.51, 1.52)
Fetal-exposed (1959–1962)	0.95 (0.64, 1.40)	0.93 (0.62, 1.39)
Childhood-exposed (1949–1958)	0.65 (0.40, 1.05)	0.62 (0.37, 1.02)
Adolescence/adult-exposed (1921–1948)	0.48 (0.22, 1.04)	0.51 (0.23, 1.13)
Non-exposed (1963–1974)	1.00 (Ref)	1.00 (Ref)
Women		
Non-exposed (1975 and later)	0.57 (0.35, 0.91)*	0.53 (0.32, 0.86)*
Fetal-exposed (1959–1962)	1.47 (1.05, 2.07)*	1.53 (1.08, 2.17)*
Childhood-exposed (1949–1958)	1.80 (1.22, 2.67)*	1.95 (1.30, 2.93)*
Adolescence/adult-exposed (1921–1948)	1.45 (0.77, 2.73)	1.57 (0.82, 3.02)
Non-exposed (1963–1974)	1.00 (Ref)	1.00 (Ref)

Data were odds ratio (95% CI), which were calculated by logistic regression models. * indicated $P < 0.05$.
Model 1 included terms for age. Model 2 included terms for age, smoking, rural/urban residence, economic status.

the results may not be generalizable to other areas and people in China. Regarding MS components, studies from Chinese and other famines also support our findings. Pre- or postnatal exposure to famine was related with higher risk of obesity [5,22,25], hyperglycemia [6–8], and hypertension in adult life [26,27].

However, there is no significant association found between famine exposure and MS in the study based on Dutch Famine [15]. The main reason might be the different duration and severity of the famine. The China's Great Famine in China haunts the memories of the Chinese people. In comparison with the Dutch Famine, the China's Great Famine lasted longer and affected more people [22]. The Dutch Famine happened between November 1944 and May 1945 [15], which means the time frame did not contain the whole gestation period. Whereas, MS components have various underlying origins and the so-called critical periods, which means organs and tissues are more susceptible to malnutrition in certain periods of rapid development. For example, microalbuminuria is related to exposure in midgestation [28] but dyslipidemia [29] and obesity [5] are associated with exposure in early gestation.

Gender-specific association was observed, but why? First, after birth, girls may suffer from severer famine. In traditional Chinese values, sons are of greater importance than daughters.

Please cite this article in press as: Wang N, et al., The famine exposure in early life and metabolic syndrome in adulthood, Clinical Nutrition (2015), http://dx.doi.org/10.1016/j.clnu.2015.11.010

When children were exposed to famine, the average welfare of the surviving girls is much worse than that of boys during childhood. Thus, preferring sons may worsen females' health outcomes including glucose and lipid metabolism in later life [11]. Second, mortality selection may be a more important factor. During famine period, male's excess mortality rate is often higher female's, particularly for fetus and infants [11]. Because of more susceptivity to adverse environmental conditions, male fetuses have a lower chance to survive [30]. The reason may be that in the uterus, boys grow more quickly and may need to retain an enlarged placenta at the cost of their own nutrition, which makes them more risky of becoming malnourished [30]. The male survivors might be healthier after famine. Thus, the mortality selection may conceal the real health consequence of the famine on male and male survivors as adults may have better metabolic outcomes as in our and previous studies [11,14].

Our study has some strengths. First, the same trained staff carried out all the data collection in each site, so this study had strong quality control. Second, our study enrolled community-dwelling men and women living in multiple sites in China, not a clinic-based population, so the results may be more representative.

Some limitations also exist. First, this is an observational study, and different age groups were taken into analysis but not the famine and non-famine exposure groups with comparable age. However, this has to be an observational study. Because the Chinese great famine swept across all the areas in China [22], we could find no place where people did not suffer from famine. Thus the reality determines the nature and method of the study. It is still a previous chance for us to look into the long-term effect of undernutrition in early life. Second, we assumed that subjects were born in the same site and did not transfer from other areas, but that might not be the case. However, although population mobility is increasing in China, permanent residency acquisition still has strict and advanced requirements and must be approved by the Chinese government. Moreover, about 97.4% of the rural population still lived in their birthplaces [7]. Thirdly, other possible confounders were not included such as birth weight, avoidance of malnutrition because of some privileges, and the dilution of some starved fetuses or infants born later than the famine exposure windows. It may not be easy to judge who were really privileges at that time. Also the privileges might be a very small part of people, which might not significantly affect the results in this large population. Moreover, this study included 1962 when population was increasing, and therefore, may have already included part of mothers who were still starving after the famine had been relieved elsewhere since 1961. However, future studies are needed to study the underlying mechanism and adjust more potential covariates to confirm this association.

In conclusion, there was a significant association between exposure to China's great famine in *utero* and during childhood (0–9 years) and MS in Chinese women, but not in men. This study also suggests the adverse effects of undernutrition might extend beyond the 'first 1000 days' and last 9 years. This may partly explain why there is such a high prevalence of MS including diabetes in China [20].

Author contributions

YL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YL and MJ were responsible for study concept and design. NW, XW and BW analyzed the data. QL, BH, YC, CZ, YC and DL acquired the data. NW drafted the manuscript, which was revised for important intellectual content by all authors. YL and MJ are guarantors.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgments

The authors thank Weiping Tu, Bin Li and Ling Hu for helping organize this investigation. This study was supported by National Natural Science Foundation of China (81270885, 81070677); Shanghai Jiaotong University School of Medicine (2014); Ministry of Science and Technology in China (2012CB524906); Science and Technology Commission of Shanghai Municipality (14495810700, 12XD1403100).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.11.010.

References

[1] Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;2014:943162.
[2] Xi B, He D, Hu Y, Zhou D. Prevalence of metabolic syndrome and its influencing factors among the Chinese adults: the China health and nutrition survey in 2009. Prev Med 2013;57:867–71.
[3] Uauy R, Kain J, Corvalan C. How can the developmental origins of health and disease (DOHaD) hypothesis contribute to improving health in developing countries? Am J Clin Nutr 2011;94(6 Suppl.):1759S–64S.
[4] Barker DJ, Osmond C, Kajantie E, Eriksson JG. Growth and chronic disease: findings in the Helsinki birth cohort. Ann Hum Biol 2009;36:445–58.
[5] Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr 1999;70:811–6.
[6] de Rooij SR, Painter RC, Roseboom TJ, Phillips DI, Osmond C, Barker DJ, et al. Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine. Diabetologia 2006;49:637–43.
[7] Li Y, He Y, Qi L, Jaddoe VW, Feskens EJ, Yang X, et al. Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. Diabetes 2010;59:2400–6.
[8] Wang N, Wang X, Han B, Li Q, Chen Y, Zhu C, et al. Is exposure to famine in childhood and economic development in adulthood associated with diabetes? J Clin Endocrinol Metab 2015 Oct 28. jc20152750.
[9] Stanner SA, Bulmer K, Andrès C, Lantseva OE, Borodina V, Poteen VV, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? results from the Leningrad siege study, a cross sectional study. BMJ 1997;315:1342–8.
[10] Lussana F, Painter RC, Ocke MC, Buller HR, Bossuyt PM, Roseboom TJ. Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. Am J Clin Nutr 2008;88:1648–52.
[11] Mu R, Zhang X. Why does the Great Chinese famine affect the male and female survivors differently? mortality selection versus son preference. Econ Hum Biol 2011;9:92–105.
[12] Johnson DG. China's great famine: introductory remarks. China Econ Rev 1998;9:103–9.
[13] Li Y, Jaddoe VW, Qi L, He Y, Wang D, Lai J, et al. Exposure to the Chinese famine in early life and the risk of metabolic syndrome in adulthood. Diabetes Care 2011;34:1014–8.
[14] Zheng X, Wang Y, Ren W, Luo R, Zhang S, Zhang JH, et al. Risk of metabolic syndrome in adults exposed to the great Chinese famine during the fetal life and early childhood. Eur J Clin Nutr 2012;66:231–6.
[15] de Rooij SR, Painter RC, Holleman F, Bossuyt PM, Roseboom TJ. The metabolic syndrome in adults prenatally exposed to the Dutch famine. Am J Clin Nutr 2007;86:1219–24.
[16] Expert Panel on Detection. Evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). JAMA 2001;285:2486–97.
[17] Lu B, Yang Y, Song X, Dong X, Zhang Z, Zhou L, et al. An evaluation of the international diabetes federation definition of metabolic syndrome in Chinese patients older than 30 years and diagnosed with type 2 diabetes mellitus. Metabolism 2006;55:1088–96.
[18] van Abeelen AF, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, et al. Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes 2012;61:2255–60.

[19] Wang N, Kuang L, Han B, Li Q, Chen Y, Zhu C, et al. Follicle-stimulating hormone associates with prediabetes and diabetes in postmenopausal women. Acta Diabetol 2015 May 12. http://dx.doi.org/10.1007/s00592-015-0769-1.
[20] Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. 2010 China noncommunicable disease surveillance group. Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948–59.
[21] Alberti KG, Zimmet P, Shaw J. IDF epidemiology task force Consensus Group. The metabolic syndrome–a new worldwide definition. Lancet 2005;366:1059–62.
[22] Luo Z, Mu R, Zhang X. Famine and overweight in China. Rev Agric Econ 2006;28:296–304.
[23] Soares GP, Brum JD, Oliveira GM, Klein CH, Souza e Silva NA. Evolution of socioeconomic indicators and cardiovascular mortality in three Brazilian states. Arq Bras Cardiol 2013;100:147–56.
[24] Zhao J, Pang ZC, Zhang L, Gao WG, Wang SJ, Ning F, et al. Prevalence of metabolic syndrome in rural and urban Chinese population in Qingdao. J Endocrinol Invest 2011;34:444–8.
[25] Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–53.
[26] Wang PX, Wang JJ, Lei YX, Xiao L, Luo ZC. Impact of fetal and infant exposure to the Chinese Great famine on the risk of hypertension in adulthood. PLoS One 2012;7:e49720.
[27] Koupil I, Shestov DB, Sparén P, Plavinskaja S, Parfenova N, Vågerö D. Blood pressure, hypertension and mortality from circulatory disease in men and women who survived the siege of Leningrad. Eur J Epidemiol 2007;22:223–34.
[28] Painter RC, Roseboom TJ, van Montfrans GA, Bossuyt PM, Krediet RT, Osmond C, et al. Microalbuminuria in adults after prenatal exposure to the Dutch famine. J Am Soc Nephrol 2005;16:189–94.
[29] Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Bleker OP. Plasma lipid profiles in adults after prenatal exposure to the Dutch famine. Am J Clin Nutr 2000;72:1101–6.
[30] Eriksson JG, Kajantie E, Osmond C, Thornburg K, Barker DJ. Boys live dangerously in the womb. Am J Hum Biol 2010;22:330–5.

Please cite this article in press as: Wang N, et al., The famine exposure in early life and metabolic syndrome in adulthood, Clinical Nutrition (2015), http://dx.doi.org/10.1016/j.clnu.2015.11.010